Remarks/Arguments:

The specification is amended, hereby, to insert the claim to domestic priority under §119(e), as required, and to insert a section of text headed "Brief Description of the Drawings."

To correct a clerical error—by changing "ultizes" to "utilizes"—a new Abstract is provided, herewith, as required.

Claims 10-25 are pending, claims 10-16 having been withdrawn pursuant to restriction.

Claims 1-9 are canceled, without prejudice or disclaimer.

Newly presented claim 17 corresponds to claim 1, amended to more clearly define the invention, as further explained below. New claims 18-25 correspond to claims 2-9, respectively, rewritten to be commensurate with changes effected—to claim 1—in claim 17 and to be dependent directly or indirectly on claim 17.

The restriction requirement was made final, and claims 10-16 withdrawn from consideration. Arguments traversing the restriction were found non-persuasive.

The argument for traversal—that Holmdahl relates to three polypeptides in a triple helix formation—is found non-persuasive because: "Claim 1 fails to recite any limitation that would convey that the epitope is in a specific structure" (Office Action, page 2).

To better convey this aspect of the invention, applicant has now limited all claims—directed to the elected subject matter—to antibodies that bind "unwound collagen type II fragments," i.e., subject matter found in original claim 11. Claim 1 is amended—as claim 17—to read (emphasis added):

> A method of qualitative or quantitative assay of **unwound collagen type II fragments containing amino acid sequence HRGYPGLDG** (SEQ ID NO: 1) in a biological sample comprising
>
> – contacting the fragments with **an antibody** that is immunoreactive with an epitope comprised in amino acid sequence HRGYPGLDG (SEQ ID NO: 1) and
>
> – detecting resulting immunoreaction.

Holmdahl is now clearly distinguished.

The PTO also finds no description of molecule Coll2-2 is provided; and, so, how applicant's remarks—with respect to Coll2-2—are relevant to the instant restriction requirement is considered unclear.

Indeed, the "remarks" at issue are not correlated with the instant claims, which do not refer to Coll2-2. Finding the examiner's question of relevance persuasive, applicant withdraws the argument at page 16, 2nd¶, of his previous reply, i.e., the paragraph ending ". . . whereas Coll2-2 is not generated as a result of collagenase activity. Further, the detection of these two peptides probably increase discriminative power of the present assay." The claims are now limited in accordance with the request of the examiner.

Additionally found non-persuasive is the argument that the binding partner of Holmdahl is capable of binding to the triple polypeptide complex and not the linear sequence SEQ ID NO: 22. The PTO reasons that the claims do not require the epitope sequence be linear and, further, that applicant has neither provided data nor cited any teaching in the reference to support the argument.

Therefore, new claim 17 combines subject matter of original claims 1 and 3, i.e., the subject matter "A method of qualitative or quantitative assay of unwound collagen type II fragments

containing all or a relevant part of the amino acid sequence HRGYPGLGDG" (claim 1) and "wherein said immunological binding partner is reactive with said epitope in the context of unwound collagen type II fragments thereof but not in the context of the wound form of these fragments" (claim 3). Figure 3 of the subject application clearly shows the assessment of the epitope Coll2-1 in the supernatants of cartilage explants cultured with clostridial collagenase A. In the corresponding experiment (Example 3, pages 16-17 of the subject application), human cartilage is digested by clostridial collagenase for a period 48 hours. The collagenase cleaves the collagen between amino acid "Y" and glycine—where "Y" is a neutral amino acid (i.e., glycine, phenylalanine, tryptophan, valine, alanine, leucine, proline, methionine, or isoleucine). In this way, native type II collagen is cut into small, linear peptides. The release of Coll 2-1 during digestion is, then, measured by immunoassay using D3 antibodies. Coll2-1 epitope is found to be released by clostridial collagenase digestion in a time-dependent manner; whereas, on the other hand, no Coll2-1 epitope is detectable in the absence of the collagenase. This finding indicates that Coll2-1 is detected by D3 in a linear, free fragment form. Further, applicant has demonstrated that antibody D3 does not recognize native (wound) collagen type II or heat-unwound collagen type II. Altogether, the data indicates that the epitope recognized by D3 is a fragment of the alpha chain, which is in a linear form. This confirmed by Deberg M., et al., "New serum biochemical markers (Coll2-1 and Coll2-1NO2) for studying oxidative-related type II collagen network degradation in patients with osteoarthritis or rheumatoid arthritis," *Osteoarthritis Cartilage, 13*, 2005, 258-65.

Further, yet, traversal based on inability of the binding partner in Holmdahl to bind present SEQ ID NO: 1 is found non-persuasive. The PTO finds no evidence or clear scientific reasoning supports the argument, rendering it non-probative as mere "opinion." Applicant respectfully disagrees.

The invention of Holmdahl is a method for detecting an antibody in a sample from a mammal (e.g., a human). The antibody specifically binds a triple polypeptide complex that contains three polypeptides, each of which contains a triple helix formation sequence. The Holmdahl method includes (a) contacting the sample with the triple polypeptide complex and (b) determining the presence or absence of the antibody bound to the polypeptide complex: a determined presence—of complex-bound antibody—indicating that the sample contains the antibody.

Therefore, first of all, the invention of Holmdahl is a method for detecting an antibody present in biological fluid in the context of autoimmune diseases. It is not a method for measuring type II collagen peptides resulting from collagen type II cleavage.

Secondly, the Holmdahl invention concerns the production of polypeptides that can be used as antigens to detect antibodies in biological fluid. Holmdahl does not describe the production of a binding partner to detect these polypeptides in biological fluid. Therefore, it is difficult for applicant to provide supporting evidence—as apparently required by the PTO—that the binding partner of Holmdahl cannot bind present SEQ ID NO: 1.

Thirdly, Holmdahl fails to demonstrate the presence, in sera of patients with autoimmune disease, of an antibody directed against SEQ ID NO: 22, which is the closest sequence to that of Coll2-1.

Fourthly, Holmdahl fails to demonstrate that SEQ ID NO: 22 can induce antibody formation, when it is injected into animals. Further, SEQ NO: 22 is not listed among the epitopes that stimulate B cells, suggesting that this sequence fails to induce antibody formation.

Altogether, the aforesaid results suggest that the antibody identified in the Holmdahl serum is not directed against SEQ ID NO: 22, which is the closest sequence to that of Coll2-1. Accordingly, the binding partner described by Holmdahl is a naturally occurring, endogenous antibody that exhibits no particular affinity/specificity for SEQ NO: 22. Holmdahl does not claim the production of a binding partner to detect a particular collagen type II sequence in biological samples.

Adding subject headings—suggested in the Office Action—is at applicant's discretion. It is not required. A specification does not necessarily lend itself to the "preferred" arrangement set forth in the Office Action. Nevertheless, applicant has inserted into the specification the sub-heading "Brief Description of the Drawings"—followed by the brief-description text, itself—support for which is found at pages 11-12 of the subject application, as filed.

Claims 1-9 are rejected under 35 USC 112, 1st ¶, for allegedly failing to comply with the written description requirement. Reconsideration is requested.

According to the statement of rejection, the rejected claims lack sufficient written description (in the specification) with respect to the subject matter: (1) "collagen type II or fragments thereof"—it being alleged that "Applicant has only described how to detect **fragments** of collagen type II that are *in the unwound form*" (Office Action, page 9,emphasis in original); (2) allegedly encompassing "detection of **all fragments** of collagen type II" (Office Action, page 9, emphasis in original)—it being alleged "the specification has only described how to detect collagen type II fragments *that have* [SEQ ID NO: 1]" (Office Action, paragraph bridging pages 9 and 10, emphasis in original); and (3) "immunological binding partner"—it being alleged that sufficient written description is provided only for "antibodies" as immunological binding partners (Office Action, page 10, second paragraph and last incomplete paragraph).

Applicant submits that present claims 17-25—replacing the rejected claims—are limited to subject matter for which the subject application satisfies the written description requirements of §112, ¶1, e.g., the written description found in Example 1 of the subject application (pages 12-14). That is, present claims 17-25 are limited (emphasis added) to a method involving

- "fragments" of "unwound collagen type II containing amino acid sequence . . . SEQ ID NO: 1" and
- "contacting the fragments with an antibody."

In view of the changes to the examined claims effected, hereby, as explained above, the rejection under §112, ¶1 for allegedly lacking adequate written description is overcome. Withdrawal of the rejection appears to be in order.

Attorney Docket No. P70086US0
Application No. 10/507,498

Claims 1-9 were rejected under 35 USC 112, 1st paragraph, for allegedly lacking enablement. Reconsideration is requested.

According to the statement of rejection, enablement is satisfied only for immunological binding partners that are "antibodies." Present claims 17-25—replacing the rejected claims—are limited to the antibody subject matter, apparently found to be enabled by the examiner.

In view of the changes effected to the rejected claims, hereby, as explained above, the rejection §112, ¶1, for alleged lack of enablement is overcome. Withdrawal of the rejection appears to be in order.

Favorable action is requested.

Respectfully submitted,

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